Remarks

I. Support for Amendments

Support for the foregoing amendments can be found throughout the specification. Specifically, support for new claims 29-38 can be found in the specification at pages 10-12; and support for the remaining amendments to the claims can be found at pages 4-5, at page 7, lines 13-17, at pages 8-12, at page 16, throughout the Examples, and in the claims as originally filed. Therefore, the foregoing amendments add no new matter, and their entry and consideration are respectfully requested.

II. Status of the Claims

By the foregoing amendments, claims 15, 20, 22, 23 and 26-28 are amended, and new claims 29-38 are sought to be entered. These amendments add no new matter. Upon entry of the amendments, claims 15-38 are pending in the application, with claim 15 being the sole independent claim.

III. Summary of the Office Action

In the Office Action dated May 3, 2002, the Examiner has maintained two rejections of the claims. Applicants respectfully traverse these rejections, and request reconsideration and withdrawal thereof. In addition, Applicants offer the following remarks concerning each element of the Office Action.

IV. The Rejection under 35 U.S.C. § 112, Second Paragraph

In the Office Action at page 2, section 4A, the Examiner has maintained the rejection of claims 15-28 under 35 U.S.C. § 112, second paragraph, as being indefinite, for reasons made of record in the previous Office Action (Paper No. 8). Applicants respectfully traverse this rejection, and reiterate and incorporate herein by reference the remarks concerning this rejection that were made in Applicants' Amendment and Reply Under 37 C.F.R. § 1.111 filed on February 4, 2002 ("the 02/04/02 reply"). Applicants also wish to offer the following additional remarks.

A. Claim 15: Effective Dose and Release Interval of IFN-γ

In maintaining this rejection, the Examiner first contends that "it is not clear if the intention of the claim is for e.g. that a 50ng dose or a 5μg dose both be released over either an 8 day period or in a I/2 [sic] hour period, or over other times in between." Paper No. 11, page 2, section 4A. Applicants respectfully disagree, and submit that there is no ambiguity regarding the dosage and release intervals that are encompassed by claim 15. Applicants first note that, contrary to the Examiner's apparent interpretation, claim 15 does not recite "a 50 ng dose *or* a 5 μg dose." Similarly, claim 15 does not recite release of the effective dose of IFN-γ over "either an 8 day period *or* in a ½ hour period." Instead, claim 15 recites the release of an effective dose of IFN-γ (which ranges from 50 ng to 5 μg) within a period of time ranging from 30 minutes to 8 days. It is simply incorrect to read the plain English of claim 15 to mean that the effective dose is exclusively 50 ng *or* 5 μg, and/or to mean that the release interval is exclusively 30 minutes *or* 8 days. As one of ordinary skill would readily understand from the plain language of claim 15, a range of dosages and release

intervals are encompassed by this claim. That is, *any dosage* amount of IFN-γ between 50 ng to 5 μg that is released over *any period* ranging from half an hour to 8 days, falls within the scope of claim 15.

As the Board has held:

> [35 U.S.C. § 112, second paragraph] merely requires that the claims set forth and circumscribe a particular area with a reasonable degree of precision and particularity. The definiteness of the claim language employed must not be analyzed in a vacuum, but always in light of the teachings of the prior art and of the particular application disclosure as it would be interpreted by one having ordinary skill in the pertinent art.

Ex parte Moelands, 3 USPQ2d 1474, 1476 (Bd. Pat. App. Int. 1987) (citing *In re Moore*, 439 F.2d 1232 (CCPA 1971). As noted above, claim 15 recites the use of an effective dose of IFN-γ ranging from 50 ng to 5 μg (both of which are easily determined using routine art-known assays) over a period of time ranging from 30 minutes to 8 days (both of which are also easily determined) Hence, one of ordinary skill could readily determine the scope of both the effective dose and the release interval that are encompassed by claim 15 as currently presented. Claim 15 thus comports with the requirements of 35 U.S.C. § 112, second paragraph, as interpreted under *Moelands* and *Moore*.

Accordingly, Applicants contend that claim 15 particularly points out and distinctly claims the subject matter regarded by Applicants as the invention. Applicants therefore respectfully request that the rejection of claim 15 under 35 U.S.C. § 112, second paragraph, be reconsidered and withdrawn.

B. Claim 26: "Tumor Cells Charged with Peptides"

The Examiner has also maintained the assertion that claim 26 is ambiguous for reciting cells that are "charged" with peptides. *See* Paper No. 11 at page 2, section 4A. Applicants contend that there is no ambiguity in the recitation of this phrase and that it would be immediately and completely understood by persons of ordinary skill in the art. However, to expedite allowance of this application and not for reasons relating to patentability or in acquiescence to this portion of the rejection, claim 26 has been amended to recite cells that "comprise" such peptides, wherein the peptides induce an immune response in an individual into whom the cells are introduced. Applicants respectfully assert that these phrases in claim 26 would readily be understood by one of ordinary skill in the art to indicate that the cells used as a source of tumor antigen-derived peptides contain the tumor antigen-derived peptides themselves. Such cells therefore include those into which such tumor antigen-derived peptides (or polypeptides, proteins or antigenic fragments thereof) have been transferred by "charging" or loading the cells with such peptides (as described in the present specification at pages 8-11). In support of this interpretation, Applicants note that methods for transporting peptides into cells for purposes of generating an immune response were well known in the art at the time of the invention. *See, e.g.*, Buschle, *et al. Proc. Nat'l. Acad. Sci. USA 94*:3256-3261 (1997) (cited as AS2 in the Information Disclosure Statement filed by Applicants on November 7, 2000, and referenced in the present specification at page 8, line 33). However, such cells also include those that naturally express tumor antigen-derived peptides, such as tumor cells that themselves express tumor antigens (as described in the present specification at pages 9-11, and throughout the Examples). Hence, the tumor vaccines of the present invention include

embodiments employing cells comprising peptides derived from tumor antigens, which are introduced into a host organism along with a source of IFN-γ, facilitating interactions between the tumor cells and the immune system of the host to produce a host immune response against the tumor antigen-derived peptides. Accordingly, Applicants respectfully assert that claim 26 is not indefinite; reconsideration and withdrawal of this portion of the rejection under 35 U.S.C. § 112, second paragraph, therefore are respectfully requested.

V. Rejection under 35 U.S.C. § 103

In the Office Action at pages 2-3, section 4B, the Examiner has next maintained the rejection of claims 15-28 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Porgador, in view of Saravolac, Cleland or Fujioka, for reasons made of record in the previous Office Action (Paper No. 8). Applicants respectfully traverse this rejection, and reiterate and incorporate herein by reference the remarks concerning this rejection that were made in the 02/04/02 reply. Applicants also wish to offer the following additional remarks.

In maintaining this rejection, the Examiner dismisses Applicants' remarks made in the 02/04/02 reply, contending that:

> Porgador clearly uses IFN-γ transected tumor cells as a source of tumor antigen, and the IFN-γ to stimulate an immune response for weak antigens. Applicant's invention is also utilizing IFN-γ to enhance the immunogenicity . . . . the use of IFN-γ along with a source of tumor antigen is to increase the immunogenicity of tumor antigens which are, in general, considered to be weak antigens.

Paper No. 11 at page 3, lines 3-6 and 13-15. Applicants respectfully note that this is *exactly* the point of Applicants' remarks made in the 02/04/02 reply: Porgador does not disclose, suggest, or otherwise contemplate the use of an IFN-γ release system that is *separate from*

the tumor antigen source. Indeed, as the Examiner clearly acknowledges in the statement above, the IFN-γ source and the tumor antigen source are *the same* in Porgador -- *i.e.*, the IFN-γ transfected tumor cells provide the IFN-γ *and* the tumor antigen for use in the methods disclosed in Porgador. This approach and its significant limitations in efficacy were well-known in the art, as is amply discussed in the present specification at pages 3-4:

> it has been shown that in order to stimulate an immune response the cytokines have to be administered within a therapeutically effective dosage window; doses of cytokine which were too low were ineffective but so were excessively high doses. On the other hand it is often difficult to achieve gene expression precisely within this effective dosage window *using the gene modification of tumour cells*, especially primary tumour cells.

Specification at page 3, line 29, to page 4, line 2 (emphasis added; internal citations omitted). Thus, as one of ordinary skill would readily understand from the teachings of the present specification, the use of IFN-γ transfected tumor cells as both the source of tumor antigen *and* the IFN-γ release system, such as the approach disclosed in Porgador, is prone to significant difficulties.

To overcome these difficulties, the present invention utilizes a system for the release of IFN-γ that is *separate from* the source of tumor antigen. The importance of this aspect of the invention is amply expressed in the specification:

> The problem of the present invention was to provide an alternative tumour vaccine which is easy to produce, which makes it possible to release the immunostimulant cytokine in [a] controlled manner at the vaccination site in the therapeutically effective dosage range over a fairly long period.
>
> This problem is solved according to the invention with a tumour vaccine based on tumour antigens, which is characterised in that it contains as active ingredient, *in addition to a tumour antigen source*, a release system with

> delayed release of the active substance for IFN-γ, the effective dosage of IFN-γ being 50 ng to 5 μg and the release interval being from half an hour to 8 days.

Specification at page 4, lines 18-31 (emphasis added). The use of separate sources for tumor antigen and IFN-γ are clearly exemplified (in a non-limiting way) in the Examples in the present specification as well, *e.g.*, in Examples 2 and 3 at pages 19-25 (using irradiated B16 melanoma cells as the tumor antigen source, and liposomes containing IFN-γ as the IFN-γ release system). As is also noted in the specification, this approach of the present invention (*i.e.*, using separate sources of tumor antigen and IFN-γ) has significant advantages over single-source approaches such as that of Porgador:

> A tumour vaccine based on tumour antigens, e.g. in the form of tumour cells, in conjunction with a "slow release" system in which IFN-γ is incorporated has the advantage, over tumour vaccines from gene-modified tumour cells which express IFN-γ [*i.e.*, the Porgador system], that the release of cytokine is precisely controlled at the vaccination site and hence the cytokine is administered in an accurate and reproducible dosage. Moreover, the labor and hence costs involved in the manufacture are substantially reduced.

Specification at page 9, line 30, to page 10, line 3. Hence, as one of ordinary skill would readily understand, the dual-source approach of the presently claimed invention is significantly different from, and has significant advantages over, the single-source approach disclosed in Porgador. Since it does not disclose, suggest or otherwise contemplate the use of a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system, Porgador is seriously deficient as a primary reference upon which to attempt to base a *prima facie* case of obviousness of the present claims.

The remaining references cited by the Examiner do not cure these deficiencies, as they also fail to teach or suggest a tumor antigen source as a separate and distinct element

from a IFN-γ delayed release system. In fact, the disclosures of Saravolac, Cleland and Fujioka are completely silent with regard to a tumor antigen source. Saravolac discloses the use of liposome-encapsulated IFN-γ *by itself* for purposes of evaluating "the effectiveness of a liposome delivery system in potentiating the antiviral as well as immunomodulatory activities of IFN-γ." *See* Saravolac at page 200, col. 2, lines 14-18. Cleland discloses the incorporation of IFN-γ into microspheres and focuses on maintaining the stability of proteins during the microencapsulation process, *i.e.*, preventing protein denaturation. *See* Cleland at page 1464, col. 1 (abstract), lines 1-7. The only implied biological use for such IFN-γ-containing microspheres in Cleland is the *in vitro* protection of cultured cells from viral killing. *See id.* at page 1466, col. 2, lines 43-56. Finally, Fujioka discloses minipelets containing "IFN." Applicants note that the interferon described in Fujioka is not IFN-γ, but IFN-α. *See* Fujioka at page 318, col. 2, lines 28-31 (". . . a natural *alpha-type* IFN, was prepared from Sendai virus-induced human Namalwa cells and purified . . . ." (emphasis added)). In addition to the fact that Fujioka does not disclose an IFN-γ release system, Applicants further note that there is no disclosure or suggestion in Fujioka that the minipellets described therein can be used in the context of a tumor vaccine.

In proceedings before the Patent and Trademark Office, the examiner bears the burden of establishing a *prima facie* case of obviousness based upon the prior art. *See In re Piasecki*, 223 USPQ 785, 787-88 (Fed. Cir. 1984). The Examiner can satisfy this burden only by showing some objective teaching in the prior art or that knowledge generally available to one of ordinary skill in the art would lead that individual to combine the relevant teachings of the references in such a way as to produce the invention as claimed. *See In re Fine*, 5 USPQ2d 1596,1598 (Fed. Cir. 1988). There is no basis for concluding that an

invention would have been obvious solely because it is a combination of elements that were known in the art at the time the invention was made. *See Fromson v. Advance Offset Plate, Inc.*, 755 F.2d 1549, 1556 (Fed. Cir. 1995). Instead, what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination. *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988). In the present case, the Examiner's burden has not been satisfied.

In sum, because none of the references cited by the Examiner discloses, suggests, or otherwise contemplates a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system, the references, alone or in combination, do not teach or suggest all of the limitations of the invention as presently claimed. As such, under *Piasecki*, *Fromson*, *Fine* and *Dow Chemical*, a *prima facie* case of obviousness has not been established.

B. There is No Suggestion or Motivation to Combine the References

Applicants have established above that the references cited by the Examiner fail to teach all of the elements of Applicants' claims. Therefore, it follows that a combination of the reference teachings would *not* lead one of ordinary skill in the art to Applicants' claimed invention. Notwithstanding this fact, Applicants also contend that neither the references themselves, nor the knowledge generally available to those of ordinary skill in the art, provide a suggestion or motivation to modify the cited references or to combine reference teachings.

The Examiner provides the following explanation as to why the skilled artisan would allegedly be motivated to combine the teachings of Porgador with that of Saravolac, Cleland or Fujioka:

> In this case, as set out both in the previous office action and the explanations above, the use of IFN-γ along with a source of tumor antigen is to increase the immunogenicity of tumor antigens which are, in general, considered to be weak antigens.

Paper No. 1, at page 3. This attempted explanation appears to misconstrue the standard for obviousness and where the required motivation must arise in order for a *prima facie* case of obviousness to be established. Applicants respectfully remind the Examiner that the requisite motivation for establishing a *prima facie* case of obviousness *must* be found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *See In re Kotzhab*, 217 F.3d 1365, 55 USPQ2d 1313 (Fed. Cir. 2000). Moreover, the mere fact that an advantage *might* be realized by combining reference teachings does not mean that a skilled artisan would be motivated to do so. *See In re Mills*, 916 F.2d 680,682, 16 USPQ2d 1430, 1432 (Fed. Cir. 1992) (Although a prior art device "may be capable of being modified to run the way the apparatus is claimed, there must be a suggestion or motivation in the reference to do so."). In the present case, rather than pointing to anything specific in the references or in the general knowledge of those skilled in the art, the Examiner has simply asserted that the use of combinations of IFN-γ and tumor antigens would be to increase the immunogenicity of tumor antigens which are weakly immunogenic. This assertion clearly misses the point, and does not provide the requisite motivation to combine the cited references. There is no dispute that the present invention is designed to increase the immunogenicity of tumor antigens -- indeed, the very goal of the present

invention is to do just that, in order to produce an effective tumor vaccine. The real issue is the approach that is taken in producing such a tumor vaccine: the art (including Porgador) uses a single-source approach where both the tumor antigen and the IFN-γ release system are located in the same source, while the present invention uses separate sources of tumor antigen and IFN-γ. There is absolutely *nothing* in Porgador or any of the other cited references that would have motivated one of ordinary skill in the art to have used a separate-source approach like that used in the present invention. Moreover, the Examiner has pointed to no acceptable objective evidence or sound scientific reasoning that would provide such motivation. Instead, the Examiner appears to *assume* that such motivation exists in the "general knowledge," without providing any basis for such an assumption. As discussed above, the requisite motivation must be found either in the prior art or in knowledge that is generally available to those of ordinary skill in the art; a baseless *assumption* of such knowledge is legally impermissible under *Fine* and *Kotzhab*. Moreover, as the Federal Circuit has held:

> [t]he range of sources available, however, does not diminish the requirement for actual evidence. That is, the showing must be clear and particular. Broad conclusory statements regarding the teaching of multiple references, standing alone, are not "evidence."

In re Dembiczak, 175 F.3d 994, 999 (Fed. Cir. 1999) (citations omitted). Since the Examiner has provided no actual evidence to support the conclusory statement that Porgador and the remaining references in combination render the present invention obvious, Applicants respectfully assert that a *prima facie* case of obviousness has not been established.

It therefore appears that the Examiner is attempting to find the required motivation to combine the cited references in Applicants' own specification rather than in the cited art. As the Federal Circuit has held numerous times, however, such a hindsight analysis is impermissible -- instead, the Examiner must show suggestions, explicit or otherwise, that would compel one of ordinary skill to combine the cited references in order to make and use the claimed invention. *See, e.g., Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1143 (Fed. Cir. 1985) ("When prior art references require selective combination by the [fact-finder] to render obvious a subsequent invention, there must be some reason for the combination other than the hindsight gleaned from the invention itself."); *Fine*, 5 USPQ2d at 1600 ("One cannot use hindsight reconstruction to pick and choose among isolated disclosures in the prior art to deprecate the claimed invention."); *In re Pleuddemann*, 910 F.2d 823, 828 (Fed. Cir. 1990) (noting that use of an applicant's specification as though it were prior art to support an obviousness determination is legal error); *In re Vaeck*, 947 F.2d 488, 493 (Fed. Cir. 1991) (holding that both the suggestion to combine references, and a reasonable expectation of success in making the claimed invention, "must be founded in the prior art, not in the applicant's disclosure."). The Board has also provided the same mandate on this issue:

> it is impermissible to use the claimed invention as an instruction manual or "template" to piece together isolated disclosures and teachings of the prior art so that the claimed invention may be rendered obvious . . . . a rejection based on § 103 must rest on a factual basis, with the facts being interpreted without hindsight reconstruction of the invention from the prior art. In making this evaluation, the examiner has the initial duty of supplying the factual basis for the rejection he advances. He may not, because he doubts that the invention is patentable, resort to speculation, unfounded assumptions or hindsight reconstruction to supply deficiencies in the factual basis.

Ex parte Haymond, 41 USPQ2d 1217, 1220 (Bd. Pat. App. Int. 1996). Thus, the use of hindsight analysis in the present case is impermissible and cannot be used to attempt to establish a *prima facie* case of obviousness.

Finally, Applicants are aware that the Examiner may consider the motivation to combine the cited references as "inherent" in the knowledge of one of ordinary skill in the art, particularly in view of the Examiner's remarks at page 3 of the present Office Action. Applicants wish to remind the Examiner, however, that there is no such thing as "inherent obviousness," since inherence and obviousness are different legal concepts. *See In re Spormann*, 150 USPQ 449, 452 (C.C.P.A. 1966). That which is inherent cannot be obvious, since inherent information "is not necessarily known . . . . [and] Obviousness cannot be predicated on what is unknown." *Id.* Since the present rejection is based on obviousness, any contention by the Examiner that is based on the possible presence of inherent knowledge in the art (either in the cited references or in the general knowledge of those of ordinary skill) must necessarily fail.

Applicants submit that, upon careful analysis of the cited references, the skilled artisan would have found no motivation to combine or modify the reference teachings to arrive at a tumor vaccine that falls within the scope of the present claims. Accordingly, a *prima facie* case of obviousness has not been established.

C. Summary

None of the references cited by the Examiner discloses, suggests or otherwise contemplates a tumor antigen source as a separate and distinct element from a IFN-γ delayed release system as required by the present claims. In addition, neither the references cited by

the Examiner nor the knowledge generally possessed by those of ordinary skill in the art provides any motivation to combine or modify the disclosures of the cited references. Thus, the criteria necessary for establishing a *prima facie* case of obviousness have not been met. Therefore, Applicants respectfully request that the rejection of claims 15-28 under 35 USC § 103(a) be reconsidered and withdrawn.

VI. Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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Version with markings to show changes made

In the Claims:

(a) Claims 15, 20, 22, 23 and 26-28 are sought to be amended as follows:

15. (Twice amended) A tumor vaccine based on tumor antigens comprising (a) a tumor antigen source; and (b) [a] an interferon-gamma (IFN-γ) release system [with delayed release of IFN-γ, the effective dose of IFN-γ being between 50 ng to 5 μg and the release interval being from half an hour to 8 days.] that is separate from said tumor antigen source, wherein said IFN-γ release system releases an effective dose of IFN-γ within a period of time ranging from 30 minutes to 8 days, said effective dose of IFN-γ ranging from 50 ng to 5 μg.

20. (Once amended) The tumor vaccine of claim 15, wherein [the] said IFN-γ release system [with delayed release of the active substance consists of] comprises liposomes containing IFN-γ.

22. (Once amended) The tumor vaccine of claim 15, wherein [the] said IFN-γ release system [with delayed release of the active substance consists of] comprises microspheres containing IFN-γ.

23. The tumor vaccine of claim 15, wherein [the] said IFN-γ release system [with delayed release of the active substance consists of] comprises minipellets containing IFN-γ.

26. (Once amended) The tumor vaccine of claim 24, wherein the tumor cells [are charged with] comprise peptides derived from tumor antigens, and wherein said peptides induce an immune response in an individual into whom said tumor cells are introduced.

27. (Once amended) The tumor vaccine of claim 15, wherein the tumor antigen source consists of antigen-presenting cells which [are charged with] comprise tumor antigen peptides, and wherein said peptides induce an immune response in an individual into whom said antigen-presenting cells are introduced.

28. (Once amended) The tumor vaccine of claim 15, wherein the tumor antigen source [consists of] comprises tumor antigens [as such] or peptides derived therefrom.

(b) New claims 29-38 are sought to be entered.